

Nelfinavir mesylate

Brand Name: Viracept



Drug Description

Nelfinavir is a nonpeptidic protease inhibitor. [1]

HIV/AIDS-Related Uses

Nelfinavir mesylate was approved by the FDA on March 14, 1997 for use in combination with other antiretroviral agents for the treatment of HIV infection.[2] [3] It is also used in conjunction with other antiretroviral agents for postexposure prophylaxis in health-care workers and other individuals exposed occupationally to blood, tissues, or other body fluids associated with a risk for transmission of HIV.[4]

Pharmacology

Nelfinavir is a selective, competitive, reversible inhibitor of HIV protease, an enzyme that plays an essential role in HIV replication. Nelfinavir is pharmacologically related to other HIV protease inhibitors but is structurally different from these and other antiretroviral drugs that are currently available. Nelfinavir's structure inhibits the function of HIV protease, interfering with the formation of essential viral proteins. The drug is active in both acutely and chronically infected cells; chronically infected cells are not affected by nucleoside reverse transcriptase inhibitors (NRTIs). While nelfinavir does not affect early stages of the HIV replication cycle, it does interfere with the production of infectious HIV, limiting further spread of the virus.

Nelfinavir is active against HIV-1 and HIV-2. Unlike nucleoside analogue antiretroviral agents, nelfinavir's antiviral activity does not require intracellular conversion to an active metabolite. Protease inhibitors, including nelfinavir, act at a different stage of HIV replication than do NRTIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs). In vitro studies indicate that the antiretroviral effects of HIV protease inhibitors and some NRTIs or NNRTIs may be synergistic.

Nelfinavir is well absorbed following oral administration, with peak plasma concentrations attained within 2 to 4 hours when 500 to 800 mg

doses are administered with food. Distribution of nelfinavir into human tissues has not been fully characterized; however, following oral administration in animals, the volume of nelfinavir distribution suggests extensive tissue distribution. Results from a study of HIV infected adults receiving nelfinavir showed no detectable concentrations of the drug in cerebrospinal fluid in samples taken from 0.5 to 10 hours after administration. Nelfinavir is more than 98% bound to plasma protein.

Nelfinavir is metabolized in the liver to many oxidative metabolites. Metabolism is mediated by several cytochrome P450 isoenzymes, including CYP3A. In patients 13 years old and older, plasma elimination half-life is 3.5 to 5 hours; in children 2 to 13 years old, nelfinavir clearance is two to three times greater than in adults. Nelfinavir is excreted principally in the feces, both as unchanged drug and metabolites.[5]

Highly variable drug exposure remains a significant problem with the use of nelfinavir in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing.[6]

Nelfinavir is in FDA Pregnancy Category B.[7] It is not known whether nelfinavir crosses the human placenta. There are no adequate and well-controlled studies to date using nelfinavir in pregnant women. Nelfinavir should be used during pregnancy only when clearly needed. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents, including nelfinavir. Physicians may register patients by calling 800-258-4263. It is not known whether nelfinavir is distributed into human milk; however, it is distributed into milk in rats.[8]

Because nelfinavir is metabolized principally by the liver, the manufacturer recommends caution when administering the drug to patients with hepatic impairment.[9]

Generally, multiple mutations are necessary for

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Pharmacology (cont.)

high level resistance to HIV protease inhibitors. Nelfinavir-resistant variants with more than one mutation have been isolated in vitro. In clinical trials, patients receiving nelfinavir had HIV variants with mutations at amino acid positions 30, 35, 36, 46, 71, 77, and 88. The principal initial amino acid change occurs at position 30 and appears to be necessary for nelfinavir resistance. In clinical studies, the overall incidence of the D30N mutation among patients receiving nelfinavir alone or in combination with NRTIs was 54.8%. The overall incidence for other mutations associated with primary resistance was 9.6% for the L90M substitution.

Clinical evidence suggests that some degree of cross resistance can occur among various HIV protease inhibitors; however, cross resistance between nelfinavir and other protease inhibitors has not been fully explored. Limited evidence suggests that mutations associated with decreased susceptibility to nelfinavir are different from those associated with decreased susceptibility to other protease inhibitors. Cross resistance between nelfinavir and NRTIs and NNRTIs is highly unlikely because these drugs target different enzymes.[10]

Adverse Events/Toxicity

Nelfinavir appears to be well tolerated; its principal adverse effects are mild to moderate diarrhea and nausea.[11] Other reactions include flatulence and rash.[12]

Body fat accumulation and redistribution, hyperlipidemia, increased bleeding in hemophilia patients, hyperglycemia, exacerbation of existing diabetes mellitus, and new onset diabetes mellitus have been reported in patients receiving protease inhibitors, including nelfinavir.[13]

Drug and Food Interactions

Presence of food in the gastrointestinal tract substantially increases absorption of oral nelfinavir. Peak plasma concentration and area under the plasma concentration-time curve (AUC) of nelfinavir are two- to threefold higher when the

drug is administered with a meal than when administered under fasting conditions.[14]

Metabolism of nelfinavir is mediated, in part, by the cytochrome P450 enzyme CYP3A. Drugs that induce this isoenzyme may reduce nelfinavir plasma concentration. Conversely, concomitant administration of nelfinavir with drugs that inhibit CYP3A may increase nelfinavir plasma concentrations. In addition, nelfinavir may alter the pharmacokinetics of other drugs that are metabolized by this enzyme system, creating the possibility of serious adverse effects. Dosage adjustments may be necessary in patients concurrently receiving nelfinavir and other drugs that are extensively metabolized by or that induce or inhibit the CYP3A isoenzyme.[15]

Concurrent use of nelfinavir with lovastatin or simvastatin is not recommended. Caution should be used when any HIV protease inhibitors, including nelfinavir, are used concurrently with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (for example, atorvastatin or cerivastatin). The resulting increased concentration of statins may increase the risk of myopathy or rhabdomyolysis.[16]

Nelfinavir should not be coadministered with astemizole, cisapride, or terfenadine (no longer available in the United States).[17]

Other drugs that should not be coadministered with nelfinavir include amiodarone, ergot derivatives, midazolam, quinidine, pimozide, rifampin, and triazolam. Nelfinavir may affect the hepatic metabolism of these drugs, creating the potential for serious or life threatening effects.

Concomitant use of products containing St. John's wort (*Hypericum perforatum*) with nelfinavir or other protease inhibitors is not recommended. St. John's wort is expected to substantially decrease plasma drug levels and may lead to loss of virologic response and possible resistance to nelfinavir or other protease inhibitors.

Caution should be used when prescribing sildenafil in patients receiving protease inhibitors, including nelfinavir. Coadministration of a protease inhibitor with sildenafil is expected to substantially increase

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Drug and Food Interactions (cont.)

sildenafil concentrations and, possibly, sildenafil-associated adverse effects, including hypotension, visual changes, and priapism.

Concomitant use of nelfinavir mesylate with certain other drugs may significantly increase or decrease plasma concentrations of nelfinavir or of the coadministered drug. Adjustment in dosage or regimen should be considered when nelfinavir is coadministered with any of the following drugs: delavirdine, indinavir, methadone, nevirapine, oral contraceptives containing ethinyl estradiol and norethindrone, rifabutin, ritonavir, or saquinavir.

Other drugs that may have a significant interaction when coadministered with nelfinavir include azithromycin, carbamazepine, cyclosporine, didanosine, phenobarbital, phenytoin, sirolimus, and tacrolimus.[18]

Contraindications

Nelfinavir mesylate is contraindicated in patients with clinically significant hypersensitivity to the drug or any components in the formulation.[19]

Clinical Trials

For information on clinical trials that involve Nelfinavir mesylate, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Nelfinavir mesylate AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[20]

Dosage Form: 250 mg and 625 mg tablets, and 50 mg nelfinavir per g oral powder.

The recommended dose of nelfinavir is 1,250 mg (five 250 mg tablets or two 625 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily. The recommended dose of nelfinavir for children age 2 years and older is 45 to 55 mg/kg per dose twice daily, or 25 to 35 mg/kg per dose three times daily.[21]

Storage: Nelfinavir mesylate tablets and powder should be stored at 15 to 30 C (59 to 86 F). Keep container tightly closed. Dispense out of original container.[22]

Chemistry

CAS Name: [3S-[2(2S*,3S*),3alpha,4abeta,8abeta]]-N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinoline carboxamide mono- methanesulfonate (salt)[23]

CAS Number: 159989-65-8[24]

Molecular formula:
C32-H45-N3-O4-S.C-H4-O3-S[25]

C59.70%, H7.44%, N6.33%, O16.87%,
S9.66%[26]

Molecular weight: 663.89[27]

Physical Description: White to off-white amorphous powder.[28]

Solubility: Soluble in water at pH of 4.0 or less; freely soluble in methanol, ethanol, isopropanol, and propylene glycol.[29]

Other Names

AG 1343[30]

NFV[31]

3-Isoquinolinecarboxamide, N-(1,1-dimethylethyl)decahydro-2-((2R,3R)-2-hydroxy-3-((3-hydroxy-2-methylbenzoyl)amino)-4-(phenylthio)butyl)-, (3S,4aS,8aS)-, monomethanesulfonate (salt)[32]

3-Isoquinolinecarboxamide, N-(1,1-dimethylethyl)decahydro-2-(2-hydroxy-3-((3-hydroxy-2-methylbenzoyl)amino)-4-(phenylthio)butyl)-, (3S-(2(2,S*,3S*),3-alpha,4a-beta,8a-beta))-, monomethanesulfonate (salt)[33]

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Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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